REMARKS

With the entry of the foregoing amended and newly added claims, claims 1, 5-35, 37, 38, 42-50, 52-59, 64 and 65 are pending in the present application. Claims 2-4, 36, 39-41, 51 and 60-63 are cancelled by this amendment.

Claims 21 and 36-38 stand rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. Claims 1-4, 8, 13-15, 18 and 33 stand rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,081,612 to Gutkowicz-Krusin et al. Claims 24, 31, and 32 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Gutkowicz-Krusin et al. Claims 5-7, 19, and 58 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Gutkowicz-Krusin et al. in view of U.S. Patent No. 5,353,790 to Jacques et al. Claims 9-12, 50, 51, 60, and 61 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Gutkowicz-Krusin et al. in view of Jacques et al. as applied to claims 6, 7 and 19 above, and further in view of U.S. Patent No. 5,784,162 to Cabib et al. The Applicants respectfully traverse these rejections. The Applicants respectfully request withdrawal of all the rejections and allowance of all pending claims in view of the foregoing amendments and for the reasons set forth below.

The Applicants also fully acknowledge that claims 16, 17, 20-23, 25-30, 59, 62 and 63 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The Applicants also respectfully acknowledge that the disclosure of U.S. Patent No. 5,986,770 to Hein et al., was considered pertinent to the Applicant's disclosure, was made of record but was not relied upon by the Examiner.

A. Amendments to Claims

Claims 1, 5, 11, 13, 21, 34, 35, 37, 38, 53, and 54 have been amended herein for clarification purposes only. Independent claims 1, 13, 34, 35, 53 have been amended herein to recite the phrase" of light remitted by a sample of tissue of known structure" or the phrase "of known structure." The Applicants respectfully submit that amended claims 1, 13, 34, 35, 53 are all fully supported by the contents of the specification as originally filed. Specifically, support for these amended claims is found for example on page 6, lines 11-17; page 10, line 14 bridging over to page 11, line 11; and page 19 lines 19-31 of the present specification. Independent claims 34 and 54 53 have been amended herein to eliminate the phrase "or

which has at least two wavelengths of which at least one is in excess of 600 nm." Also, claim 34 has been amended for clarity to delete the phrase "along the or each line or at each point" and add the phrase "which includes at least one of a line, a point, and a combination thereof", support for which can be found for eample on page 8, lines 5-10 of the present specification. Dependent claims 2-4, 36, 39-41, 51 and 60-63 have also been cancelled without prejudice to simply avoid any redundant claims in light of the claim amendments recited above. Also, dependent claims 5, 11, and 37 have been amended to simply correct the dependency of the claims in light of the claim amendments recited above. The Applicants respectfully submit that no new matter was added to the application.

B. Newly added claims

New independent claims 64 and 65 have been added herein for clarification purposes only. The Applicants respectfully submit that new claims 64 and 65 are fully supported by the contents of the specification as originally filed. Specifically, support for independent claims 64 and 65 can be found, for example, at page 6, last paragraph of the specification. The Applicants respectfully submit that no new matter was added to the application.

C. Rejection of Claims

Rejections Under 35 USC §112

Claims 21 and 36-38 stand rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. The Applicants submit that in response to the rejections asserted in the Office Action, claim 21 has been amended to depend on claim 18, where the calibration step was originally recited. Also, in response to a rejection for insufficient antecedent basis with respect to the limitation "said record." in claims 36-38, Applicants submit that claim 36 has been cancelled, and claims 37 -38 have been amended to recite the limitation "datum sample" instead of the term "record". Also, claim 34 has been amended to delete, among other amendments the phrase, "or having at least two wavelengths of which at least one is in excess of 600 nm". The above amendment is made for clarification purposes only and not for reasons of patentability. No new matter has been added. Therefore, the Applicants respectfully submit that based on the amendment of the subject claims, the rejection has been obviated.

Rejections Under 35 USC §102

Claims 1-4, 8, 13-15, 18, 33, 35, 39-49 and 52-57 stand rejected under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,081,612 to Gutkowicz-Krusin et al. The Office Action characterizes the Gutkowicz-Krusin et al. reference, among other things, as disclosing systems and methods for non-invasive spectral imaging and characterization of skin tissue. The method includes illuminating an area of skin with light from three spectral bands and digitally imaging the area of skin with remitted light. The digital images are comprised of digital signals whose values are functions of the skin condition. The images are processed and segmented by a processor. The processor outputs the condition of the skin by estimating values of skin parameters and comparing a weighted combination of these values to a threshold value. The threshold value may come from a training set of images that exemplify skin conditions (column 3, lines 53-67; column 4, lines 1-25). The Office Action further asserts that the spectral bands used in the method of Gutkowicz-Krusin et al. comprise the center wavelength ranges of: 350-500 nm; 500-600 nm; and 750-1000 nm (column 4, lines 51-56).

The Office Action further asserts that the apparatus of Gutkowicz-Krusin et al. includes a light source (3), a photo-receptor (6), processing means to perform applications such as comparing variations (12), a filter wheel (29), polarization means both for illumination light and remitted light (31 and 31a), means to pass a control signal to a display device (12), means to carry out illumination in various spectral bands (4 and 27), means to monitor remitted light intensity (6 and 12), means for a flexible light guide (30a and 30b), and means to further carry out the methods of Gutkowicz-Krusin et al.

The Applicants respectfully submit that for the most part the Office Action correctly summarizes the operation of the Gutkowicz-Krusin et al. However, the Applicants submit that it is more accurate to characterize Gutkowicz-Krusin et al. as describing a method and apparatus for multispectral imaging and characterization of skin tissue to give automatic characterization of the condition of a region of interest of the skin. An area of skin is illuminated with light and the remitted light forms a digital image of the skin. The digital images are made up of digital signals whose values are functions of the skin condition. The series of multispectral digital images are processed to produce a series of parameter values – by carrying out a calculation based upon weighted parameter values and then comparing against a threshold value, a diagnosis about the condition of the skin can be made. The

threshold value has been pre-calculated by studies of a number of different lesions (i.e., abnormal skin), forming a training set of images.

The Applicants submit that in contrast, the present invention focuses on a method of analyzing tissue where particular images of tissue are compared and referenced against a sample of tissue of a known structure, that is the concentration of a melanin in the epidermis, and the concentration and location of melanin, blood and collagen in the papillary dermis. The reference tissue is a normal tissue of a known structure. Furthermore, Gutkowicz-Krusin et al., differs from the present invention in that the present invention does not automatically provide a diagnosis. The present invention provides an image compared with the tissue of known structure to allow a clinician to make a diagnosis. Gutkowicz-Krusin et al., purely provides a weighted parameter calculation that is compared with a threshold value to provide an automatic diagnosis. (See page 6, lines 11-17; page 10, line 14 bridging over to page 11, line 11; and page 19 lines 19-31 of the present specification.) The training set of images is made up of abnormal tissues i.e. lesions.

Also, the Applicants submit that claim 13 is directed towards a method of analyzing tissue structure, not as disclosed by Gutkowicz-Krusin, a method of calibrating its system by correcting tissue color co-ordinates using the white target (See paragraph 7 of the Office Action). Also, in amended claim 13, the color co-ordinates are compared with a co-ordinate range for healthy tissue of a known structure, whereas in contrast, Gutkowicz-Krusin only references a threshold value calculated from a training set of skin abnormalities.

In addition to the comments set forth above, the Applicants submit that in addition to independent claim 13, independent claims 1, 35, and 53 have been amended to recite that the reference sample is generally a normal healthy tissue of known structure. The above amendments are made for clarification purposes only and not for reasons of patentability. No new matter has been added. Therefore, the Applicants respectfully submit that based on the amendment of the subject claims, the rejection has been obviated.

Rejections Under 35 USC §103

Claims 24, 31, and 32 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Gutkowicz-Krusin et al. The Office Action asserts that the method of Gutkowicz-Krusin et al. involves imaging the skin. The Office Action also asserts that Gutkowicz-Krusin et al. refers to a calibration sequence used to calibrate the images in order to eliminate

such effects as variation in illumination pattern or aging in the lamp (column 11, lines 32-36). The Office Action further asserts that it would be obvious to one having ordinary skill in the art to calibrate an image for comparison with another image that was acquired under different conditions in order to achieve unbiased results.

The Applicants respectfully submit that in view of the clarifying amendment to independent claim 13 from which claims 24, 31, and 32 all depend, Gutkowicz-Krusin et al., is not prior art under §§ 102/103 and would not be an enabling reference. The method and apparatus of Gutkowicz-Krusin et al., suggests and teaches a processor that compares a weighted combination of parameter values against a threshold value for an abnormal tissue or lesion such as a melanoma multiple times to provide an automatic diagnosis. In contrast, the present invention does not automatically provide a diagnosis. Instead, the present invention provides an image compared with the tissue of known structure to allow a clinician to make a diagnosis. (See page 6, lines 11-17; page 10, line 14 bridging over to page 11, line 11; page 19 lines 19-31 of the present specification). Thus, Gutkowicz-Krusin et al., should not be used as the basis for any rejection.

Claims 5-7, 19, and 58 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Gutkowicz-Krusin et al. in view of U.S. Patent No. 5,353,790 to Jacques et al. The Office Action asserts that the method of Gutkowicz-Krusin et al. includes comparing the remitted light from the area of interest to reference data and the reference data does not come from a mathematical optical model of the tissue. The Office Action also asserts that Jacques et al. disclose a method and apparatus for the optical measurement of bilirubin in tissue where the method includes using an optical model of the skin to develop parameters for an algorithm to determine the amount of cutaneous bilirubin. (See column 3, lines 5-36). Furthermore, the Office Action asserts that it would be obvious to one having ordinary skill in the art to use the model of Jacques et al. with the method of Gutkowicz-Krusin et al. because Gutkowicz-Krusin et al. seek to distinguish abnormal skin from normal skin, and parameters derived from a mathematical model of normal skin would be useful to compare with acquired parameters from an area of interest in order to characterize the area of interest and minimize errors that could occur from miscalibration or random variations occurring during data acquisition. Also, the Office Action asserts that the method of Jacques et al. includes a measurement of the melanin level in order to eliminate the effects of melanin on the data for bilirubin (figure 37A). The Office Action further asserts that it would be obvious

to one having ordinary skill in the art to use the measurement from the Jacques et al. method with the skin tissue characterization method of Gutkowicz-Krusin et al. in order to eliminate the effects of melanin so that the dermal structure could be analyzed.

The Applicants respectfully submit that Gutkowicz-Krusin et al., in view of Jacques et al., does not render claims 5-7, 19 and 58 obvious, because it would not be obvious to combine the teachings of Gutkowicz-Krusin and Jacques et al., to make the present invention. In general, the Applicants submit that Jacques et al. discloses a method for determining an arterial blood oxygen saturation level. More specifically, Jacques et al., discloses a method and apparatus for determination of bilirubin concentration in tissue, in particular neonatal skin tissue. The apparatus is also used to calculate maturity of neonates. The method only relates to the study of bilirubin. Also, a model of normal skin is used as a reference, however, there is no teaching or suggestion of modeling of an abnormal skin.

The Applicants further submit that it would not be obvious to combine the teachings of Gutkowicz-Krusin and Jacques et al., because the system of Gutkowicz-Krusin depends on a training set of abnormalities and lesions. Therefore, in the event that Gutkowicz-Krusin ever contemplated any improvements to the system, they would be taught away from Jacques et al., which teaches the use of a model of healthy skin only (and is directed towards neonates and for the purpose only of bilirubin detection).

In light of the claim amendments to claims 1, 13, 34, 35, 53 and the discussions set forth herein above, Jacques et al., does not make up for the deficiencies in teaching or suggestion in Gutkowicz-Krusin et al., with respect to the fact that the system of the present invention always uses a datum sample of a tissue of known structure - not a weighted threshold value based upon a series of studied lesions. Absent a primary reference, Jacques et al., alone is not sufficient to make a *prima facie* case of obviousness because Jacques et al. does not teach all the limitations. Accordingly, any disclosures of the secondary reference, Jacques et al., is not sufficient to make a *prima facie* case of obviousness. The Applicants respectfully request withdrawal of the rejection of the claims under 35 USC §103(a).

Claims 9-12, 50, 51, 60, and 61 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Gutkowicz-Krusin et al. in view of Jacques et al. as applied to claims 6, 7 and 19 above, and further in view of U.S. Patent No. 5,784,162 to Cabib et al. The Office Action asserts that the combined Gutkowicz-Krusin et al. and Jacques et al. reference does

not include means for controlling a treatment process. The Office Action asserts that Cabib et al. describes methods of spectral bio-imaging. The Office Action also asserts that using the modified Gutkowicz-Krusin et al. reference to control and predict PDT would be obvious to one having ordinary skill in the art because using spectral bio-imaging in conjunction with PDT was a known method at the time of the application.

The Office Action asserts that Cabib et al. discloses an application of spectral bio-imaging for cancer tissue mapping for diagnosis and analysis before, during and after an operation, and to visualize the borders of diseased tissue during an operation. The Office Action asserts that it would be obvious to one having ordinary skill in the art to use the endoscopic configuration of Cabib et al. with the method of Gutkowicz-Krusin et al. in order to analyze and monitor internal epithelial and sub-epithelial tissue.

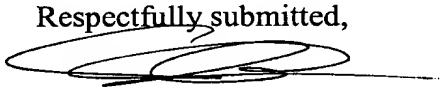
The Applicants respectfully submit that in light of the claim amendments (specifically, cancellations of claims 60-63) and discussions recited hereinabove, neither the primary reference Gutkowicz-Krusin et al., nor the Jacques et al., teaches or suggests the claims of the present invention. Absent a primary reference, Gutkowicz-Krusin et al., alone is not sufficient to make a *prima facie* case of obviousness because Gutkowicz-Krusin et al. does not teach all the limitations. Accordingly, any disclosure of secondary references Jacques et al. and Cabib et al., is not sufficient to make a *prima facie* case of obviousness. Hence, the present invention is not obvious over Gutkowicz-Krusin et al., in view of Jacques et al., and further in view of Cabib *et al.* Accordingly, the Applicants respectfully request withdrawal of the rejection of the claim 36, under 35 USC §103(a).

In addition to other bases for allowability of new claims 63 and 64, the Applicants respectfully submit that the foregoing remarks, comments, and arguments rebut any *prima facie* case of lack of written description, nonenablement indefiniteness, novelty, or non-obviousness with respect to these claims.

IV. SUMMARY

Based on the foregoing, the Applicants respectfully submit that pending claims 1, 5-35, 37, 38, 42-50, 52-59, 64 and 65 of the present application are in condition for allowance, and a favorable action thereon is respectfully requested. Should the Examiner feel that any other point requires consideration or that the form of the claims can be improved, the Examiner is invited to contact the undersigned at the number listed below.

Respectfully submitted,



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MARKED UP VERSION SHOWING CHANGES

All the words, phrases, or numbers Applicants propose to add are underlined, and all words, phrases, and numbers Applicants propose to [remove] therefrom are enclosed in brackets ("[ ]"):

1. (Once Amended) A method of monitoring the presence of one or more chromophores in a sample of biological tissue, which method comprises illuminating an area of such tissue sample by projecting light from a light source, receiving light remitted by the illuminated area of tissue at a photo-receptor, spectroscopically analyzing the remitted light, and comparing variations in the intensity and spectral characteristics of the remitted light with respect to the intensity and spectral characteristics of the projected light and with data representing a datum sample of intensity and spectral characteristics of light remitted by a sample of tissue of known structure, and emitting a control signal in response to any such variations.

5. (Once Amended) A method according to claim [4]1 of deriving data relating to the presence and/or depth and/or concentration of any chromophore selected from the group consisting of: melanin, blood, haemoglobin, oxy-haemoglobin, bilirubin, tattoo pigments and dyestuffs, keratin, collagen and hair.

11. (Once Amended) A method according to claim [4]1 applied for endoscopic monitoring of the presence of one or more said chromophores in the tissue sample.

13. (Once Amended) A method of non-invasively analyzing structure, comprising the steps of:

(i) measuring red or infrared radiation from at least one location in an area of tissue under investigation so as to give an indication of any layered structure in said area;

(ii) measuring the tissue color co-ordinates at said at least one location in said area of tissue;

(iii) using data obtained in measuring steps (i) and (ii) to calculate corrected tissue color co-ordinates in respect of said area which corresponds to a predetermined thickness of said layered structure, and;

(iv) comparing the corrected tissue color co-ordinates obtained in step (iii) with a reference color co-ordinate range for healthy tissue having a known layered structure of the same predetermined thickness.

21. (Once Amended) A method according to claim [17] 18, wherein said calibration in step (vi) includes estimating the level of epidermal melanin levels calculated within at least one normal skin region adjacent said location.

34. (Once Amended) A method of mapping the papillary surface of an area of the dermis which comprises illuminating the surface of the skin over that area with light and monitoring the intensity of light remitted from along at least one line or sequence of points, the light having a wavelength sufficiently far into the infrared that its absorption by melanin and blood is negligible, [or having at least two wavelengths of which at least one is in excess of 600nm] and deriving therefrom a theoretical intensity of remitted light which is independent of the presence of melanin or blood, and from the remitted light intensity deriving a signal corresponding to the concentration of collagen within the papillary dermis which includes at least one of a line, a point, and a combination thereof, [along the or each line or at each point], and producing a contoured image in which the apparent elevation of any point is dependent upon the strength of such signal.

35. (Once Amended) Apparatus for monitoring the presence of one or more chromophores in a biological tissue sample, which apparatus comprises a light source for projecting light to illuminate an area of such tissue sample, a photo-receptor for receiving light remitted by the illuminated area of tissue, and a spectroscopic analyzer for monitoring the remitted light, a comparator for comparing variations in the intensity and spectral characteristics of the remitted light with respect to the intensity and spectral characteristics of the projected light at different wavelengths and with data representing a datum sample of intensity and spectral characteristics of light remitted by a reference sample of tissue of known structure and a signal emitter for emitting a control signal in response to any such variations.

37. (Once Amended) Apparatus according to claim [36]35, wherein said [record] datum sample is a [record] datum sample of intensity and spectral characteristics of light remitted by a reference sample of skin.

38. (Once Amended) Apparatus according to claim 35, wherein said [record] datum sample is a [record] datum sample of the intensity and spectral characteristics of light remitted by a reference sample of normal healthy tissue.

53. (Once Amended) Apparatus for non-invasively analyzing skin structure, comprising: means for projecting UV and/or visible and/or red and/or infrared radiation onto an area of skin under investigation, measuring means for measuring remitted red or infrared radiation from at least one location over said area of skin so as to give an indication of the collagen thickness in said area; skin color coordinate measuring means for measuring the skin color coordinates at said at least one location in said area of skin; calculating means for using data obtained in measuring steps (i) and (ii) to calculate corrected skin color coordinates in respect of the or at least one said area which corresponds to a predetermined amount of collagen, and; color comparison means for comparing the corrected skin color coordinates obtained in step (iii) with a reference color coordinate range for skin of known structure with the same collagen content.

54. (Once Amended) Apparatus for mapping the papillary surface of an area of the dermis which comprises a light source illuminating the surface of the skin over that area with light which [either] has a wavelength sufficiently far into the infrared that its absorption by melanin and blood is negligible, [or which has at least two wavelengths of which at least one is in excess of 600 nm] means for monitoring the intensity of the light remitted along at least one line or sequence of points, and deriving therefrom an intensity or theoretical intensity of remitted light which is independent of the presence of melanin or blood, and means for deriving a signal from the remitted light intensity corresponding to the concentration of collagen within the papillary dermis along the or each line or at each point, and for producing a contoured image in which the apparent elevation of any point is dependent upon the strength of such signal.